REMARKS

Reconsideration of the rejections set forth in the Office Action mailed May 23, 2005 is respectfully requested. Claims 28, 32-41, and 45-49 are pending. Claims 28, 38, and 41 are currently amended. Claims 30 and 43 are canceled. The applicant petitions the Commissioner for a 1-month extension of time: a separate petition accompanies this amendment.

I. Amendments

In accordance with the Examiner's comments on page 2 of the Office Action mailed May 23, 2005, independent claims 28 and 41 have been amended to recite the structure noted by the Examiner. This amendment is made in the interest of expediting prosecution. Applicants reserve the right to pursue the broader claim scope in continuing applications.

II. Rejections under 35 U.S.C. §103(a)

Claims 28, 30, 32-41, 43 and 45-49 (all pending claims) were rejected under 35 U.S.C. §103(a) as being unpatentable over Zalewski *et al.*, U.S. Patent No. 6,159,946, in view of Kobayashi *et al.* (*Osaka Daigaku Zasshi* **47**(6-12), Abstract, 1995), Summerton *et al.* (U.S. Patent No. 5,378,841), Agrawal *et al.* (U.S. Patent No. 5, 912,332), and Burger (WO 98/46740).

A. The Invention

The Applicant's invention, as embodied in independent claim 28, is directed to a method of treating a vascular injury site in a patient by reducing restenosis at the site. The method comprises administering to the patient, by intravascular delivery directly to the vascular injury site, a morpholino antisense compound having uncharged phosphorodiamidate intersubunit linkages, as recited in independent claim 28.

As discussed previously, a recently completed Phase II clinical study, described in a Declaration by co-inventor Dr. Dwight Weller, showed efficacy in a patient population having existing recurrent restenosis following PTCA, and selected based on criteria targeting patients with a high probability of restenosis. As shown in the

Declaration, patients receiving an anti-c-myc morpholino oligomer, as set forth in the claims, showed significantly less reocclusion than patients receiving a subtherapeutic dose or receiving no oligomer. No drug-related serious adverse effects were observed.

B. The Cited Art

Zalewski *et al.*, cited previously, discloses the use of a phosphorothioate-linked oligonucleotide targeting c-myc mRNA in an *in vivo* porcine model of coronary angioplasty. The data showed that the oligonucleotide "significantly reduced neointimal formation" in this animal model (Example 11). The cited reference does not, however, disclose efficacy of the phosphorothioate oligonucleotide in a human patient.

Kobayashi *et al.* discloses a phosphorothioate-linked oligonucleotide having a 27-nucleotide sequence which includes the 20-nucleotide sequence disclosed by the applicants as SEQ ID NO:1. The phosphorothioate oligonucleotide of Kobayashi was reported to suppress the tumor growth of gastric cancer cells and colon cancer cells transplanted in nude mice.

Summerton *et al.* discloses uncharged-backbone morpholino oligomers and their benefits over native RNA or DNA oligonucleotides as antisense agents.

Agrawal *et al.* is cited for its disclosure of a triethylene glycol solubility-enhancing group.

Burger teaches the use of a morpholino oligomer having a nucleotide sequence directed to CMV (cytomegalovirus) for inhibition of restenosis.

It is noted that Burger contains no specific data, either *in vitro* or *in vivo*, regarding suppression of restenosis (see discussion below in Part D.).

Overall, none of the foregoing references, all of which were cited previously, provide any guidance or expectation of success as to suppression of restenosis in a human patient.

C. The Weller Declaration

The above-referenced Weller Declaration, submitted on May 1, 2002, pointed out that a clinical trial employing the phosphorothioate oligonucleotide disclosed in Zalewski *et al.* failed to show any efficacy in inhibiting post-PTCA restenosis in a patient population (as reported in Kutryk *et al.*, *J. Amer. Coll. Cardiology* **39**:281-7, 2002, enclosed with the response dated May 1, 2003).

Upon further consideration, the Examiner stated that the evidence presented in this Declaration "is not considered commensurate in scope with the claimed invention." Each of the Examiner's particular arguments is addressed in turn below.

1. Limitation to the particular oligomers used in the Weller Declaration

With regard to the Weller Declaration, the Examiner contends that "claim 28 is not limited to the particular oligomers used in the Weller Declaration," (Office Action mailed May 23, 2005, page 3).

In accordance with the Examiner's suggestions, claim 28 now recites a method for treating a vascular injury site in a human patient by reducing restenosis at the site, said method comprising, administering to the patient, by intravascular delivery directly to the vascular injury site, a morpholino antisense compound having uncharged phosphorodiamidate intersubunit linkages where $X=N(CH_3)_2$, Y=O, and Z=O; and comprising the sequence identified as SEQ ID NO: 1, in an amount effective to reduce restenosis in the patient. This amendment is made in the interest of expediting prosecution. Applicants reserve the right to pursue the broader claim scope in continuing applications.

2. Limitation to the particular concentration of antisense compound used in the Weller Declaration

With regard to the Weller Declaration, the Examiner has also stated that it is not commensurate in scope with the claimed invention because "claim 28 is not limited to ... the particular concentration of antisense compound used in the Declaration," (Office Action mailed May 23, 2005, page 3).

Applicants disagree with the Examiner's requirement that a "particular concentration" of antisense compound be recited in the claims.

Case law has established that the common claim phrase "an effective amount" may or may not be indefinite. The proper test is whether or not one skilled in the art could determine specific values for the amount based on the disclosure. (MPEP 2173.05(c)III, May 2004 edition; citing *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975).

The phrase "an effective amount" has been held to be indefinite when the claim **fails** to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. However, in the present case, the function to be achieved is clearly stated in the independent claims.

In re Fredericksen 213 F.2d 547, 102 USPQ 35 (CCPA 1954). The more recent cases have tended to accept a limitation such as "an effective amount" as being definite when read in light of the supporting disclosure and in the absence of any prior art which would give rise to uncertainty about the scope of the claim. In *Ex parte Skuballa*, 12 USPQ2d 1570 (Bd. Pat. App. & Inter. 1989), the Board held that a pharmaceutical composition claim which recited an "effective amount of a compound of claim 1" without stating the function to be achieved was definite, particularly when read in light of the supporting disclosure which provided guidelines as to the intended utilities and how the uses could be effected. (MPEP §2175.05(c)III).

Here, a person of ordinary skill in the relevant art would have adequate guidance as to the preferred and appropriate methods of delivery directly to the vascular injury site, of a morpholino antisense compound. For example, Applicants' written description provides a detailed disclosure of different methods of delivery currently available and used in the art. See, for example, the specification at page 11, line 5, through page 14, line 23; describing different methods of delivery of an antisense compound to the vessel site, including recommended amounts for each of these delivery methods. One skilled in the art would be familiar with these delivery methods. Given the particular disclosure in the specification, containing preferred and suggested amounts of the compound to be delivered, Applicants maintain that there is no need to recite an exact concentration of antisense compound in the claims themselves.

Moreover, it is well established that "claims are not to be read in a vacuum, and limitations therein are to be interpreted in light of the specification in giving them their 'broadest *reasonable* interpretation.'" *In re Okuzawa*, 537 F.2d 545, 548 (CCPA 1976). Based on the cited case law, as well as the applicable provisions of the MPEP, Applicants maintain that there is no requirement that the claims be amended to recite the particular concentration of antisense compound used in the Declaration. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC § 103(a) based on these grounds.

3. Requirement for "identical conditions"

With regard to the Weller Declaration, the Examiner has also stated that "the experiments set forth in the declaration do not include the appropriate controls, such that it would be clear that the same *identical conditions* were used in the controls as those used to produce the unexpected results asserted for the claimed morpholino phosphorodiamidate antisense compounds" (Office Action mailed May 23, 2005, pages 3-4). Further, the Examiner contends that "in order to properly judge whether or not Applicant's results are truly unexpected over the prior art, applicants must provide evidence that in a side by side comparison, using identical conditions, the full scope of the claimed methods using morpholino modified phosphorodiamidate antisense compound comprising SEQ ID NO:1, unexpectedly produce (*sic: produced*) a greater reduction in restenosis in comparison to the prior art phosphorothioate modified antisense compound comprising SEQ ID NO:1" (Office Action mailed May 23, 2005, pages 3-4).

Applicants disagree that evidence produced "in a side by side comparison," allegedly "using identical conditions," is required to properly judge whether or not Applicants' results are truly unexpected over the prior art. Applicants know of no such requirement. Rather, the MPEP, at § 716.02(e), states that "[a]n affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a prima facie case of obviousness," *In re Burckel*, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). "Where the comparison is not identical with the

reference disclosure, deviations therefrom should be explained," *In re Finley*, 174 F.2d 130, 81 USPQ 383 (CCPA 1949).

Here, Applicants note that the conditions employed in the AVI BioPharma Inc., Phase II clinical study, and those employed in the Kutryk clinical study (Kutryk *et al.*, *J. Amer. Coll. Cardiology* **39**:281-7, 2002), were actually not that dissimilar. For example, (1) both studies used balloon angioplasty, followed by stent implantation; (2) both studies used a patient population having existing restenosis; (3) both studies employed 10 mg of oligomer; and (4) both studies delivered the oligomer using a balloon catheter. In addition, both studies ran a control where no oligomer was used.

Applicants note that it is highly unlikely, if not impossible, to expect that two clinical trials by different investigators would involve *identical* conditions. Due to the expense of conducting a clinical trial, it is unlikely that the Applicants could recreate the exact experimental conditions as those found in a clinical trial carried out by other investigators. Such a requirement would be unduly burdensome and impractical.

The Examiner has further noted that "there are no control oligonucleotides representing the prior art modified oligomers under the same conditions as those used to produce the asserted unexpected results..." (Office Action mailed May 23, 2005, page 4).

Again, it would be unduly burdensome for applicants to conduct a clinical trial in human patients simply for the purpose of comparison with a competitive product, particularly when the purpose of the trial is, of course, to obtain regulatory approval for the applicants' product.

The MPEP, at 716.02(g) III, further states that "[a]lthough evidence of unexpected results must compare the claimed invention with the closest prior art, applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art" (see MPEP 700-263).

In a good faith effort, Applicants have compared their experimental results to the closest subject matter that is known to exist. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC § 103(a) based on these grounds.

D. Indications of Nonobviousness: Failure of others and long felt need

As discussed in the previous response, the CAFC held, in *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988), that "Recognition of need, and difficulties encountered by those in the field, are classical indicia of unobviousness."

As stated in a preliminary report assessing the safety and pharmacokinetics of the Zalewski oligonucleotide (Roque *et al.*, *Antisense & Nucleic Acid Drug Dev.* **11**:99-106, 2001; copy enclosed with response of May 1, 2003), "Coronary restenosis remains a vexing clinical problem" (page 99, Introduction). The paper notes some of the associated difficulties, including the "more complex human atherosclerotic lesions" as compared to porcine coronary arteries in model studies (paragraph bridging pages 103-104).

The review article "Restenosis: a challenge for pharmacology" (H. Bult, *Trends in Pharmacological Sciences* **21**:274-279, July 2000; copy enclosed) states that "Finding effective therapies to combat restenosis has been difficult because of the incomplete understanding of the biology of restenosis and the lack of suitable animal models" (first paragraph). Under "Further limitations of animal models" (page 274), it states that "The response to injury in healthy arteries might follow a very different course of events from the clinical reality in the abnormal human coronary arteries that exhibit complex intimal lesions".

Another review article, "Novel approaches for the prevention of restenosis" (L. Gruberg *et al., Expert opinion on investigational drugs* **9**(11):2555-78, Nov 2000; summary enclosed) states that "Despite intensive investigation in animal models and in clinical trials, most pharmacological agents have been found to be ineffective in preventing restenosis after percutaneous balloon angioplasty or stenting. Although studies frequently report success in the suppression of neointimal proliferation in animal models of balloon vascular injury, few of them have been successful in clinical trials."

An editorial in *Annals of Vascular Surgery*, entitled, "Intimal Hyperplasia—Still Here after All These Years!" (K. Craig Kent, *et al., Annals of Vascular Surgery*, **18**(2):135-37, Mar 2004; copy enclosed) reiterates that in 2004, "[a] number of drugs that have been tested in human clinical trials have failed." The article notes that it is not as though researchers in this field "haven't tried." In particular, Table I contains a

summary of "over 30 drugs or molecular therapies that have been effective in preventing IH in animals (the actual list includes over 100 agents)," suggesting, at a minimum, that humans and rats differ with respect to claudication. Further, the review indicates that experiments in animal models have been discouraging. Specifically, "in a phase II clinical trial designed to treat restenosis following coronary stenting, c-myc antisense was administered via a dual-balloon infusion system. The results at 6 month were discouraging and revealed that treatment with c-myc antisense did not reduce IH." (Here, the trial referred to was the Kutryk *et al.* study referred to in the Weller Declaration.)

Thus, the impression in the art, several years after the time of filing, was that coronary restenosis in the clinical setting was a longstanding and intractable problem, and that success in an animal model did not necessary transfer to success in human patients at risk for restenosis. Today, it is still perceived as such a problem.

It is also noted that the therapeutic approach described in Burger targets the DNA of an exogenous virus (CMV), which is completely different from the target of the present claims, an endogenous proto-oncogene (c-myc). Suppression of expression of these sequences would be expected to produce different physiological effects on a molecular level. Even though the targeted disease state is the same, the two treatment approaches are completely different. The teachings of Burger therefore would not provide any expectation of success in the use of an antisense oligomer targeting c-myc for suppression of restenosis in a patient, particularly in view of the overall state of the art, as discussed above.

Accordingly, the combination of Zalewski *et al.*, which shows the effect of a phosphorothioate-linked anti-c-myc oligonucleotide in an animal model of restenosis, and Burger *et al.*, which teaches the use of an anti-CMV morpholino oligomer, without supporting data, would not provide a reasonable expectation that the presently claimed oligomers would effectively inhibit restenosis at a vascular injury site in a patient, as demonstrated by the data presented in the Weller Declaration.

In view of the foregoing, the applicants respectfully request the Examiner to withdraw the rejections under 35 U.S.C. §103(a).

III. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4341.

Respectfully submitted,
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Editor's Commentary

Intimal Hyperplasia—Still Here after All These Years!

Despite the many recent technological advances in vascular intervention, intimal hyperplasia (IH) remains an expensive, morbid, and unsolved problem. It is estimated that hyperplastic lesions lead to failure of 5-30% of vascular reconstructions including angioplasty, although the actual rate varies with each procedure. IH forms as a result of a cascade of molecular and cellular events triggered by the injury that accompanies vascular reconstruction. The release of a number of vasoactive, thrombogenic, and mitogenic factors, through mechanisms not completely understood, stimulates vascular smooth muscle cells to proliferate, migrate, and produce extracellular matrix. The end-product is a highly cellular, subintimal lesion that narrows the vessel lumen (for more detailed review on molecular mechanisms of IH, see Newby and Zaltsman[1]). IH is ubiquitous and not always consequential. Following carotid endarterectomy, almost all patients develop a smooth, uniform, recurrent lesion that is unlikely to embolize, and becomes problematic only if there is progression to a severe stenosis. Alternatively, even a modest amount IH in a 3-mm femoral-tibial vein graft leads to occlusion and failure of the bypass. The overall impact of IH on the durability of our vascular interventions is profound and thus it is imperative that methods to control this process be developed.

It is not that we haven't tried. Table I is an abbreviated list of over 30 drugs or molecular therapies that have been effective in preventing IH in animals (the actual list includes over 100 agents). So why so little success? The simple answer is that rats are different from humans; they are smaller and don't have strokes, heart attacks, or claudication. The complete explanation, however, is much more complex. Many antagonists of IH that have been evaluated in animals have been shown to produce a statistically significant response but not one that is numerically relevant. In our clinical practices, a drug that statistically inhibits IH by only 30%, even if this were a significant response, would likely be of little use. The duration of a drug's inhibitory effect is also an important consideration. A one-time application of an antagonist might lead to a reduction in the early hyperplastic response that develops at 2 weeks. But what happens at 6 months when the drug is no longer available but the stimulus for hyperplasia persists? The mechanism of IH appears to differ with each intervention. Thus, drugs that prevent IH after angioplasty may not be effective for prosthetic grafting or visa versa. Drug delivery persists as a major problem. It remains difficult to control the concentration of drug released and the duration of delivery. The use of adenoviral techniques to deliver inhibitors in humans at one time seemed "around the corner" but is clearly still a number of years away. The list of problems goes on and on.

So where are we in 2004? A number of drugs that have been tested in human clinical trials have failed. Several pharmacological agents such as aspirin, ticlopidine, clopidogrel, and warfarin, which have a demonstrable effect on thrombosis, have little or no effect on neointimal hyperplasia. Recently, however, drug-eluting stents have gained a great deal of attention. Stents coated with a polymer matrix that locally deliver high doses of therapeutic reagents over time have been found to be efficacious in preventing restenosis after coronary angioplasty. Drugs currently under evaluation include anticancer agents such as actinomycin D, paclitaxel, and vincristine, as well as immunosuppressants such as sirolimus, everolimus, and tacrolimus. Sirolimus (or rapamycin) is a macrolide antibiotic with antifungal and immunosuppressive properties that, in vitro, is a potent inhibitor of smooth muscle cell proliferation and migration.[2,3] Several recent large prospective studies have shown a substantial reduction in coronary restenosis in patients treated with rapamycin-coated stents.[4-6] However, sirolimus-eluting stents have not been as effective in preventing restenosis in peripheral vessels such as the superficial femoral artery.[7] The reasons for this are unclear. The superficial femoral and coronary arteries are quite different, and so is the disease that affects these vessels. Atherosclerosis is focal in the coronary circulation and diffuse in the femoral artery. It is now clear that before rapamycin or other agents become effective inhibitors of IH in peripheral vessels, there will need to be further adjustment in the mode or duration of drug delivery.

Intravascular radiation or brachytherapy is another approach that has been tried in humans. Human trials using beta or gamma radiation resulted in a significant reduction in IH after coronary

Table I. Agents that inhibit intimal hyperplasia in animal models.

α-Adrenergic inhibitors	Heparins	17-β-Estradiol	βARKct	p16
ACE inhibitor	Iloprost	7-Hexanoyl-taxol	Anti-PDGF	p21
Aspirin	Nimodipine	Actinomycin D	Anti-TGF-β	p27
Ca channel blockers	Ornithine decarboxylase inhibitor	Batimastat	bcl	p53
Captopril	Prazosin	Dexamethasone	*c-myc*	ras
Cilazapril	Suramin	Everolimus	COX	Rb
Cyclosporine	Thromboxane synthetase inhibitor	Paclitaxel	E2F decoy	TIMP
Clopidogrel	Ticlopidine	Sirolimus	eNOS	TK
Cilostazol	Trapidil	Tacrolimus	Fas ligand	TPA
Elastase	Verapamil	Vincristine	iNOS	VEGF
Enalapril	Warfarin		NF-κB	

ACE, angiotensin-converting enzyme inhibitor; βARKct, C-terminal β–adrenergic receptor kinase; COX, cyclooxygenase; NF-κB, nuclear factor κB; PDGF, platelet-derived growth factor; Rb, retinoblastoma; TGF-β, transforming growth factor β; TIMP, tissue inhibitor of metalloproteinase; TK, thymidine kinase; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; TPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor.

stenting, which prompted the U.S. Food and Drug Administration (FDA) to approve brachytherapy for the treatment of in-stent restenosis of the coronary arteries.[8,9] But the clinical benefits of brachytherapy have been tempered by the development of restenosis in regions adjacent to the target site (candy wrapper effect) and also by late thrombotic events. Moreover, the procedure is expensive, and at times inconvenient, and it requires the services of a radiation oncologist. Longer follow-up of patients is necessary before the efficacy of brachytherapy can be fully measured.

A variety of molecular therapies designed to inhibit IH are currently under clinical evaluation. In an exciting area of research, the use of small molecules called "decoys" in the prevention of IH is under investigation. In vivo, proteins called "transcription factors" bind to DNA and initiate transcription of target genes. Decoys are short sequences of DNA that can bind transcription factors and thus act as a sink, sequestering these proteins so that they are not available to activate genes. A decoy has been created that blocks the E2F transcription factor, which is responsible for activating multiple genes responsible for smooth muscle cell proliferation. Human trials have been initiated to evaluate the ability of the E2F decoy to prevent vein graft failure following coronary and peripheral bypass. In these trials, E2F decoys are administered intraluminally into explanted saphenous veins using a pressure device. In a phase II trial of coronary bypass, one-time administration of the E2F decoy led to an approximately 30% reduction in a composite index of vein graft failure and death.[10] A smaller single-institution trial has demonstrated a similar positive effect in E2F-treated peripheral bypass grafts.[11] Patient enrollment in phase III trials of both coronary and peripheral bypass has recently been completed but the outcome of these trials is still more than a year away.

In animal models, the infusion of *c-myc* antisense has resulted in significant inhibition of IH.[12] Antisense oligonuclotides inhibit gene expression by binding to messenger RNA and thus preventing translation of RNA into protein. Since c-myc protein is necessary for vascular smooth muscle cell proliferation, blocking c-myc translation has the potential to interfere with the formation of IH. In a phase II clinical trial designed to treat restenosis following coronary stenting, *c-myc* antisense was administered via a dual-balloon infusion system. The results at 6 months were discouraging and revealed that treatment with *c-myc* antisense did not reduce IH.[13]

Gene transfer, often mediated by viral vectors, has been shown to be an effective method for inducing or blocking the expression of genes that can inhibit IH. Despite the overwhelming success with this technique in animals, few human gene therapy trials have been designed. The slow progress in adapting this technique for human use is related to a lack of efficient viral vectors, concerns about the safety of intraarterial gene therapy, and the lack of efficient methods of delivering virus. In a recent phase II trial, adenoviral-mediated gene transfer of vascular endothelial growth factor (VEGF) following coronary angioplasty and stenting did not result in a diminution in the rate of restenosis.[14] However, this study did demonstrate the safety of intracoronary gene transfer via an adenoviral vector. In other phase I trials, plasmid-based gene transfer of endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) are being evaluated as inhibitors of IH in the peripheral as

well as the coronary circulation. Although it is too early to predict the outcome of these and other trials, such studies provide hope that vascular gene therapy for restenosis will eventually become a practical and potentially effective option.

The need to prevent or control the hyperplastic response that develops following peripheral vascular interventions is great. Although drug-eluting stents appear to offer a promising treatment for restenosis following coronary interventions, drug-coated stents are not the final answer. Stents are costly and the efficacy of drug-coated stents in the peripheral circulation has not been proven. In this post-genomic era, molecular therapies, although still in their infancy, could emerge as the method of choice for the delivery of inhibitory agents. Ultimately, an oral agent would be the most efficient and least costly treatment for IH. We are still years and many research dollars away from finding the final solution to a significant problem that frequently affects our practice of vascular surgery.

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REFERENCES

1. Newby AC, Zaltsman AB. Molecular mechanisms in intimal hyperplasia. J. Pathol. 2000;190:300-309.
2. Marx SO, Jayaraman J, Go LO, Marks AR. Rapamycin-FKBP inhibits cell cycle regulators of proliferation in vascular smooth muscle cells. Circ. Res. 1995;76:412-417.
3. Poon M, Marx SO, Gallo R, Badimon JJ, Taubman MB, Marks AR. Rapamycin inhibits vascular smooth muscle cell migration. J. Clin. Invest. 1996;98:2277-2783.
4. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N. Engl. J. Med. 2003;349:1315-1323.
5. Regar E, Serruys PW, Bode C, et al. Angiographic findings of the multicenter randomized study with the sirolimus-eluting Bx velocity balloon-expandable stent (RAVEL): sirolimus-eluting stents inhibit restenosis irrespective of the vessel size. Circulation 2002;106:1949-1956.
6. Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. Circulation 2001;104:2007-2011.
7. Duda SH, Pusich B, Richter G, et al. Sirolimus-eluting stents for the treatment of obstructive superficial femoral artery disease: six-month results. Circulation 2002;106:1505-1509.
8. Waksman R, Raizner AE, Yeung AC, Lansky AJ, Vandertie L. Use of localised intracoronary [beta] radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. Lancet 2002;359:551-557.
9. Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. N. Engl. J. Med. 2001;344:250-256.
10. Terashima M, Grube E, Takahashi T, et al. Intraoperative cell-cycle blockade using E2F decoy for prevention of early atherosclerosis in coronary bypass vein graft: a volumetric IVUS subanalysis from a prospective randomized double blind clinical trial. J. Am. Coll. Cardiol. 2002;39:228A.
11. Mann MJ, Whittemore AD, Donaldson MC, et al. Ex-vivo gene therapy of human vascular bypass grafts with E2F decoy: the PREVENT single-centre, randomised, controlled trial. Lancet 1999;354:1493-1498.
12. Kipshidze NN, Kim HS, Iversen P, et al. Intramural coronary delivery of advanced antisense oligonucleotides reduces neointimal formation in the porcine stent restenosis model. J. Am. Coll. Cardiol. 2002;39:1686-1691.
13. Kutryk MJ, Foley DP, van den Brand M van den , et al. Local intracoronary administration of antisense oligonucleotide against c-myc for the prevention of in-stent restenosis: results of the randomized investigation by the Thoraxcenter of antisense DNA using local delivery and IVUS after coronary stenting (ITALICS) trial. J. Am. Coll. Cardiol. 2002;39:281-287.
14. Hedman M, Hartikainen J, Syvanne M, et al. Safety and feasibility of catheter-based local intracoronary vascular endothelial growth factor gene transfer in the prevention of postangioplasty and in-stent restenosis and in the treatment of chronic myocardial ischemia: phase II results of the Kuopio angiogenesis trial (KAT). Circulation 2003;107:2677-2683.

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